UNITED STATE DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/491,982	01/27/00	SHAUGHNESSY S	1171-101

028120
ROPES & GRAY
ONE INTERNATIONAL PLACE
BOSTON MA 02110-2624

HM12/0716

EXAMINER	
PRASAD,S	
ART UNIT	**PAPER NUMBER**
1646	9

DATE MAILED: 07/16/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/491,982	Shaughnessy et al.	
	Examin r	Art Unit	
	Sarada C Prasad	1646	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *19-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

Detailed Action

1. Applicant's election with traverse of Group I (claims 1-18, 40,41) in Paper No. 7 (5/7/01) is acknowledged. The traversal is on the ground(s) that Groups I and II are so closely related and they share common features that would facilitate searching both Groups at once. However, this argument is not found persuasive because invention of Group II claiming to administer effective amounts of transcribable genetic material to inhibit the formation of ternary complex of IL-11, IL-11R and gp130 involves gene therapy methods, involves patient follow up which is unlike in Group I where in peptides, or peptidomimetics, or small compounds are administered to achieve inhibition of formation of ternary complex of IL-11, IL-11R and gp130. A search for methods of treatment of osteoporosis by gene therapy would not be complete when carried out along with a search for therapy of osteoporosis by other methods that include administration of peptides or small compounds.

Therefore, the restriction requirement is still deemed proper and is therefore made FINAL. Currently claims 1-18, 40 and 41 are under consideration by the Examiner.

Specification

2a. A portion of page 28 is blank.

2b. Numbering of SEQ ID No in the claims, in the specification, and in the Figures is inconsistent, for example: in claims 13 and 32 sequences are recited in three letter code; in brief description of Figures peptides 1 and 2 are identified as SEQ ID NOs: 1 and 2 (see page 6, Figure 4); Figure 4, peptides 1 and 2 are referred to as SEQ ID NOs 1 and 2 as a side-note in pencil.

2c. There are no bolded amino acids in Figure 3 as stated, however, there are bolded amino acids in Figure 4,when not mentioned as such. Appropriate correction is required.

2d. Claim 13 has no sequence identifier. Polypeptides greater than 5 amino acid residues in length must be referenced by SEQ ID No. Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st para-scope

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of treating or alleviating the symptoms of osteoporosis-associated postmenopausal bone loss comprising inhibiting, in a mammalian patient suffering from such a condition, the formation of a ternary complex of IL-11, IL-11R and gp 130 by administering (i) soluble IL-11R mutants with at least one mutation in its gp 130 binding region selected from D282-G282, A283-D283, G286-D286, H289-Y289, V291-L291.....; or (ii) an antibody to IL-11; or (iii) an IL-11 binding peptide that specifically binds in the region normally bound by IL-11R characterized as RRLRASW; (iv) an antibody to IL-11R inhibiting the interaction of IL-11R and IL-11; (vi) an antibody to IL-11R which inhibits the interaction of IL-11 and gp 130, does not reasonably provide enablement for a process of treating or alleviating the symptoms of 'all other pathological condition in which bone density is decreased' comprising inhibiting the formation of a ternary complex between IL-11, IL-11R, and gp 130 by administering 'other IL-11 antagonists', 'other IL-11R antagonists', or 'other IL-11 binding

peptides', or 'other IL-11R binding peptides' or 'unidentified small molecules' that can inhibit formation of a ternary complex between IL-11, IL-11R and gp 130. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3a. Claim 1 reciting 'a process of treating or alleviating the symptoms of a pathological condition in which bone density is decreased....' is overly broad. The claim language encompasses situations not described in the specification that my result in 'pathological conditions with as resulting decrease in bone density' other than postmenopausal bone loss. It is not feasible for a skilled artisan to administer the instant 'substance' to inhibit the formation of a ternary complex between IL-11, IL-11R and gp 130 to those who might have a pathological condition of bone loss due to reasons other than postmenopausal causes. No guidance is provided in the specification as to what other causes precipitate bone loss and if the instant 'osteoporosis cure' would be beneficial. The instant specification disclosed approaches for inhibiting bone resorption associated with osteoporosis. However, what are the several other diseases in which bone loss is one of the characteristics? Each of the symptoms of a particular disease may have to be treated with a different approaches, for example the instant method of inhibiting ternary complex formation of IL-11, IL-11R and gp 130 to achieve inhibition of osteoclast formation is for that particular symptom irrespective of the nature of the disease. It requires undue experimentation to realize the situation and then try if osteoporosis treatment worked for other forms of bone loss.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, is it undue (In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404).

Therefore, considering the breadth of claim 1, state-of-the-art, guidance provided in the specification, the amount of experimentation required is undue to practice the invention as claimed. Therefore, the specification is non-enabling for practice of claims 1-18 and 40-41.

3b. Recitation of 'effective amount of a substance which inhibits, *in vivo* the formation of ternary complex...' in claim 2 is overly broad. What is the nature of 'a substance' which inhibits the formation of the ternary complex between IL-11, IL-11R and gp130. Several reagents including antibodies, binding peptides directed against IL-11, or IL-11R or gp 130 in addition to several unnamed small molecules, have the potential of being that 'a substance' that inhibits the formation of the ternary complex between IL-11, IL-11R and gp130. It is not feasible for a skilled artisan to practice the claimed invention with all these substances. The mechanism of action of these different agents is not necessarily identical and inhibition of ternary complex formation *in vivo* in the presence or absence of 'a substance' as claimed is not predictable. It requires undue experimentation to administer such a substance to all those who have any form of pathological condition that leads to bone loss and hence the specification is non-enabling for practice of this claim 2.

3c. Recitation of 'mutant IL-11R' in claim 4 is overly broad because it is not possible to test all possible mutations through out the entire sequence of IL-11R or even in the region of IL-11R sequence that can bind to IL-11. Methods to prepare a mutant with altered sequence at one amino acid residue do not necessarily provide all the information needed to prepare other mutants. Furthermore, mutants with amino acid changes at any other position would not yield polypeptides with desired characteristics such as being able to inhibit the formation of the ternary complex by occupying the specific site on the IL-11R that would inhibit IL-11 from binding at

that site. It requires undue experimentation to find out which mutants other than the soluble IL-R mutants described at residues 282, 283, 286, 289, and 291 would be able to bind to IL-11, and inhibit the ternary complex formation. Therefore, the specification is non-enabling for a person of skill in the art to practice claim 4.

3d. Recitation of 'an IL-11 binding peptide' in claims 11 and 12 is extremely broad and encompasses several classes of molecules that fit the description of a 'IL-11 binding peptide'. The specification is enabled for a binding peptide with a selected region representing its receptor binding region of the sequence 'RRLRASW'. However, the disclosure is non-enabling for other binding peptides of IL-11 that have not been envisioned. It requires undue experimentation to find out 'what is included,' and 'what is not included' in the list of such 'IL-11 binding peptides' with no sequence description at hand, for example: out of the two peptides tested in Example 5 of the instant disclosure, peptide 2 was not effective (lines bridging pages 29-30). Therefore, practice of claims 11 and 12 is nonenabled.

3e. Recitation of 'a small molecule' in claim 14 is extremely broad in that the nature of such a small molecule is left open for determination by the skilled artisan. No guidance is provided as to what are the small molecules that are allowed and not allowed? what should be their chemical nature, and what should be their mode of action, is it via binding to any of the three components of the ternary complex, such as IL-11, or IL-11R or gp 130 or changing the cellular environment where the complex formation occurs. It is not possible for the skilled artisan to practice the claimed invention with unnamed small molecules to treat osteoporosis. It requires undue experimentation to find out what are those small molecules that fit the claimed invention.

3f. Recitation of 'IL-11 antagonist' in claim 15 is overly broad in encompassing IL-11 mutants, or IL-11antibodies, or short binding peptides IL-11, or IL-11R binding peptides . The specification is enabled for an anti-IL-11 antibody, 'RRLRASW' region of IL-11R that IL-11 can bind to and not 'any other IL-11 antagonists' and not for other uncharacterized, unnamed IL-11 antagonists. Therefore, the specification is non-enabling for the practice of the claim 15.

3g. Recitation of 'IL-11R binding peptide' in claim 16 is extremely broad without describing the specifically whether 'the binding peptide' is a portion of the IL-11R antibody, or a portion of the IL-11. It is well known in the art that any number of polyclonal antibodies directed to certain epitopes still may be lacking in antibodies directed to certain other epitopes while each monoclonal antibody is directed only to one epitope. Therefore, without providing guidance as to the specificity of the antibodies with respect to its antigen binding site, a general 'IL-11R binding peptide' would not be able to efficiently block the formation of a ternary complex formation. Therefore, the specification is not enabled to practice the instant invention as claimed in claim 16.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, is it undue (In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404). Therefore, considering the breadth of claims 1, state-of-the-art, guidance provided in the specification, the amount of experimentation required is undue to practice the invention as claimed. Claims 2-18 are rejected insofar as they depend on claim 1.

Claim Rejections - 35 USC § 112-second para

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-18, 40-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claims 1, 40, 41 recite use of acronyms such as IL-11, IL-11R, and gp130. Use of acronyms can be subject to change, or same acronym could be used for more than one compound. Therefore, the acronyms need to be spelled out completely when first used, and then referred to by the abbreviations appropriately. This rejection can be obviated by reciting interleukin-11, interleukin-11 receptor, and glycoprotein 130 in claim 1.

4b. Claims 40, 41 recite 'a composition of matter' 'comprising an antibody.....'. A composition of matter consists of more than one ingredients and not just one antibody. This rejection can be obviated by reciting 'a composition comprising an antibody.....' .

4c. Claim 13 recites a peptide comprising the sequence 'Arg Arg Leu Arg Ala Ser Trp'. Peptides longer than five amino acids in length need to be referenced by SEQ ID Nos. This rejection can be obviated by referencing the sequence with a SEQ ID NO.

4d. Claim 1 recites no method steps, for example inhibition of ternary complex formation inhibits osteoclast formation without positive recitation of the steps necessary to inhibit the complex formation. Appropriate correction is required.

4e. Claims 40 and 41 recite 'interaction' between IL-11 and IL-11R or IL-11R and gp 130 respectively. It is not clear as to what is meant or included by 'interaction' other than binding.

4f. Claim 14 is vague and indefinite in reciting 'the substance is a small molecule' because it is not clear as to what is the definition of a small molecule in selecting a compound for the claimed invention. This rejection can be obviated by reciting the nature of the small molecule.

4g. Claim 15 is vague and indefinite in reciting 'IL-11 antagonist'. It is common practice to refer to compounds as receptor antagonists not as ligand antagonists which would be receptors themselves. This rejection can be obviated by reciting how this instant 'IL-11 antagonist' is different from IL-11R itself.

Claims 2-18 are rejected insofar as they depend on claim 1.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-18 and 40, 41 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9619574.

WO 9619574 teaches methods of inhibiting binding of IL-11 to the human IL-11R in a mammalian subject which comprise administering a therapeutically effective amount of a composition containing a human IL-11R protein, an inhibitor, or an antibody to a human IL-11R protein (last 3 lines of page 6). WO 9619574 also teaches methods of treating or preventing loss of bone mass in a mammalian subject using these compositions (first 3 lines of page 7). Instant claims 1-9, and 15-18, 40, 41 reciting a process of treating postmenopausal bone loss,

comprising inhibiting ternary complex formation of IL-11, IL-11R and gp 130, comprising administration of antagonists of IL-11, either peptidomimetics or antibodies directed to IL-11R are anticipated.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-18, 40, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Romas et al. (1995) in view of WO 9619574.

Romas et al. teach that the gp130-coupled IL-11 plays a central role in osteoclast development (see abstract, lines 16-17). Furthermore, Romas et al. also teach that formation of multinucleated osteoclast-like cells (OCLs) in response to IL-11, or IL-6 together with its soluble IL-6 receptor was dose dependently inhibited by rat monoclonal anti-mouse gp130 antibody (see abstract, lines 9-11; page 2582, column 1, and pages 2587-2589 discussion; and Figure 7).

Disclosure of Romas et al. also taught use of antibodies to IL-11 for inhibition of osteoclast formation as well (page 2582, column 1, 2nd para, lines 8-10) and *in vitro* biological assays for IL-11, IL-11R (see materials and methods, bridging pages 2582-3). However, Romas et al. did not teach *in vivo* use of these reagents for treatment of osteoporosis, and use of soluble IL-11R mutants.

WO 9619574 teaches human IL-11R and inhibitors of binding of IL-11 and IL-11R in addition to compositions comprising antibodies to IL-11R, and inhibitors of binding of IL-11 and IL-11R. Disclosure of WO 9619574 also teaches methods of identifying an inhibitor to the human IL-11R. The substances according to WO 9619574 are useful in the treatment of bone loss, for eg. postmenopausal bone loss (see abstract, page 6, lines 1-page 7, line 3; page 14, line 14-page 17 line 2; page 22, line 10-14 and the claims). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to combine the teachings of Romas et al. and WO 9619574 and conclude that (i) measures to inhibit formation of osteoclasts would result in an increase in bone density; (ii) agents that inhibit the interaction between IL-11, IL-11R and gp 130 inhibit osteoclast formation, and hence would be beneficial for the treatment of osteoporosis.

Therefore, it would have been prima facie obvious to develop a process of treating or alleviating the symptoms of postmenopausal bone loss by inhibiting formation of ternary complex between IL-11, IL-11R and gp130 by administering antagonists of IL-11 and IL-11R and gp 130, thus rendering instant claims obvious.

Conclusion

7. No claims are allowed

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday - Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
July 10th, 2001

Yvonne Eyler

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600